

FORM PTO-1390 (Modified)
(REV 11-98)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

**TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371**

210227US0XPCT

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

09/869129

INTERNATIONAL APPLICATION NO.

PCT/JP99/07161

INTERNATIONAL FILING DATE

20 DECEMBER 1999

PRIORITY DATE CLAIMED

24 DECEMBER 1998

TITLE OF INVENTION

AGENT FOR TREATING VISUAL CELL FUNCTION DISORDER

APPLICANT(S) FOR DO/EO/US

Ryuji UENO

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
 - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☒ has been transmitted by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ Certificate of Mailing by Express Mail
20. ☒ Other items or information:

Request for Consideration of Documents Cited in International Search Report**Notice of Priority**

PCT/IB/304

PCT/IB/308

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR <div style="font-size: 1.5em; font-weight: bold;">09/869129</div>		INTERNATIONAL APPLICATION NO. <div style="font-weight: bold;">PCT/JP99/07161</div>		ATTORNEY'S DOCKET NUMBER <div style="font-weight: bold;">210227US0XPCT</div>	
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21. The following fees are submitted: BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) : <div style="margin-left: 20px;"> <input type="checkbox"/> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$1,000.00 <input checked="" type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$860.00 <input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$710.00 <input type="checkbox"/> International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$690.00 <input type="checkbox"/> International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) \$100.00 </div> <div style="text-align: right; margin-top: 10px;"> ENTER APPROPRIATE BASIC FEE AMOUNT = </div> <div style="margin-top: 10px;"> Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492 (e)). </div> <table border="1" style="width:100%; border-collapse: collapse; margin-top: 5px;"> <tr> <th style="width:15%;">CLAIMS</th> <th style="width:20%;">NUMBER FILED</th> <th style="width:20%;">NUMBER EXTRA</th> <th style="width:10%;">RATE</th> <th style="width:15%;"></th> <th style="width:10%;"></th> </tr> <tr> <td>Total claims</td> <td>11 - 20 =</td> <td>0</td> <td>x \$18.00</td> <td></td> <td>\$0.00</td> </tr> <tr> <td>Independent claims</td> <td>3 - 3 =</td> <td>0</td> <td>x \$80.00</td> <td></td> <td>\$0.00</td> </tr> <tr> <td colspan="4">Multiple Dependent Claims (check if applicable).</td> <td><input checked="" type="checkbox"/></td> <td>\$270.00</td> </tr> <tr> <td colspan="5" style="text-align: right;">TOTAL OF ABOVE CALCULATIONS =</td> <td>\$1,130.00</td> </tr> <tr> <td colspan="5">Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) (check if applicable).</td> <td><input type="checkbox"/> \$0.00</td> </tr> <tr> <td colspan="5" style="text-align: right;">SUBTOTAL =</td> <td>\$1,130.00</td> </tr> <tr> <td colspan="5">Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).</td> <td>+ \$0.00</td> </tr> <tr> <td colspan="5" style="text-align: right;">TOTAL NATIONAL FEE =</td> <td>\$1,130.00</td> </tr> <tr> <td colspan="5">Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable).</td> <td><input type="checkbox"/> \$0.00</td> </tr> <tr> <td colspan="5" style="text-align: right;">TOTAL FEES ENCLOSED =</td> <td>\$1,130.00</td> </tr> <tr> <td colspan="5"></td> <td>Amount to be: refunded \$</td> </tr> <tr> <td colspan="5"></td> <td>charged \$</td> </tr> </table>				CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE			Total claims	11 - 20 =	0	x \$18.00		\$0.00	Independent claims	3 - 3 =	0	x \$80.00		\$0.00	Multiple Dependent Claims (check if applicable).				<input checked="" type="checkbox"/>	\$270.00	TOTAL OF ABOVE CALCULATIONS =					\$1,130.00	Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) (check if applicable).					<input type="checkbox"/> \$0.00	SUBTOTAL =					\$1,130.00	Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).					+ \$0.00	TOTAL NATIONAL FEE =					\$1,130.00	Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable).					<input type="checkbox"/> \$0.00	TOTAL FEES ENCLOSED =					\$1,130.00						Amount to be: refunded \$						charged \$	CALCULATIONS PTO USE ONLY	
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☒ A check in the amount of **\$1,130.00** to cover the above fees is enclosed.

☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees.
 A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **15-0030** A duplicate copy of this sheet is enclosed.

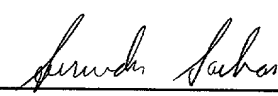
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:



22850

Surinder Sachar
Registration No. 34,423


 SIGNATURE

Norman F. Oblon
 NAME

24,618
 REGISTRATION NUMBER

6-25-01
 DATE

DESCRIPTION**AGENT FOR TREATING VISUAL CELL FUNCTION DISORDER****TECHNICAL FIELD OF THE INVENTION**

The present invention relates to an agent for treating visual cell function
5 disorder.

BACKGROUND OF THE INVENTION

In the structure of the eye, retina is present in the eyeground and controls the function of the eye to recognize the presence or absence and shape of an object by the presence of a visual cell layer of retina. In recent years, patients with eye
10 diseases undergo objective test of retinal function by the determination of electroretinogram (hereinafter sometimes referred to merely as ERG) and the determination is utilized for the diagnosis of the condition. The ERG consists of a-wave, b-wave, c-wave and the like, and a-wave is considered to mainly reflect the function of visual cells, b-wave is considered to reflect the function of bipolar cell
15 layer (mainly Müller cells) and c-wave is considered to reflect the function of retinal pigment epithelium. When the retinal function is damaged for some reason, it appears as changes in the peak latency and amplitude of each wave. For example, in the case of diabetic retinopathy, it is known that peak latency of each wave is extended from the early stage and the amplitude is attenuated; all waves are
20 attenuated and disappear in degenerative disease of retina, such as pigmentary retinal degeneration; and each wave becomes attenuated depending on the stages of disease in retinoblastoma disorder such as central retinal artery occlusion, central retinal vein thrombosis, fundus hypertonicus, retinal detachment and the like. While the b-wave and the like are originated from the source located more
25 toward the central side of the retina than the visual cell from which the a-wave is originated, when the light reaches the retina, the visual cell is first excited and the b-wave and the like are first generated when the excitement is transmitted to the retinal cells on the central side. Therefore, even when the source of origin is other than visual cell, the waves are under strong influence of the function of the visual
30 cell. In other words, when the function of visual cell is damaged, ERG components become abnormal even if the source of origin of the b-wave and the like is normal. Therefore, in ERG, a-wave is the most important component, and if changes in peak latency and amplitude of a wave, which are caused by the

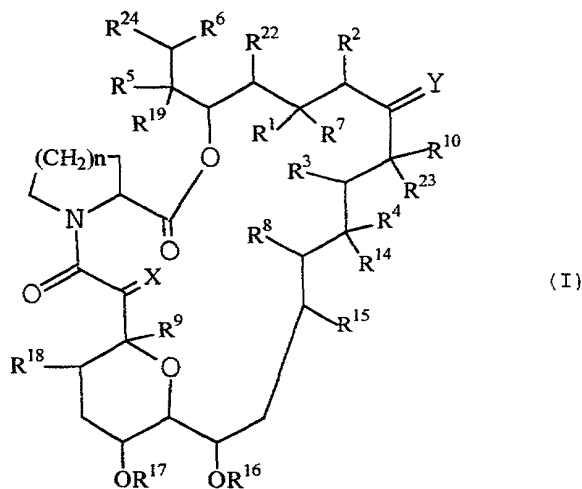
damaged function of visual cell, can be suppressed or recovered, the visual cell function disorder is expected to be effectively treated.

SUMMARY OF THE INVENTION

The present inventor has conducted intensive studies and surprisingly found that interleukin 2 (hereinafter sometimes referred to simply as IL-2) inhibitor has superior improving effect on visual cell function disorder and exhibit superior therapeutic effect on the diseases associated with visual cell function disorder, which resulted in the completion of the present invention.

Accordingly, the present invention provides the following.

- (1) An agent for treating visual cell function disorder comprising an interleukin 2 inhibitor as an active ingredient.
- (2) The agent of (1), wherein the interleukin 2 inhibitor is a macrolide compound or a cyclosporin.
- (3) The agent of (2), wherein the macrolide compound is a tricyclo compound (I) of the following formula



wherein adjacent pairs of R^1 and R^2 , R^3 and R^4 , and R^5 and R^6 each independently

- a) consist of two adjacent hydrogen atoms, wherein R^2 is optionally alkyl, or
- b) form another bond optionally between carbon atoms binding with the

members of said pairs ;

R^7 is hydrogen atom, hydroxy, protected hydroxy or alkyloxy, or may form oxo with R^1 ;

R^8 and R^9 each independently show hydrogen atom or hydroxy ;

R¹⁰ is hydrogen atom, alkyl, alkyl substituted by one or more hydroxy, alkenyl, alkenyl substituted by one or more hydroxy or alkyl substituted by oxo ;

X is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula -CH₂O- ;

5 Y is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula N-NR¹¹R¹² or N-OR¹³ ;

R¹¹ and R¹² each independently show hydrogen atom, alkyl, aryl or tosyl ;

R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²² and R²³ each independently show hydrogen atom or alkyl ;

10 R²⁴ is an optionally substituted ring that may contain one or more hetero atom(s) ; and

n is 1 or 2.

In addition to the meaning noted above, Y, R¹⁰ and R²³ may show, together with the carbon atom they bind with, a saturated or unsaturated 5 or 6-membered
15 heterocyclic group containing nitrogen atom, sulfur atom and/or oxygen atom, the heterocyclic group being optionally substituted by one or more group(s) selected from alkyl, hydroxy, alkyloxy, benzyl, a group of the formula -CH₂Se(C₆H₅), and alkyl substituted by one or more hydroxy, or a pharmaceutically acceptable salt thereof.

20 (4) The agent of (2) or (3), wherein the macrolide compound is FK506.

(5) The agent of any of (1) to (4), which is used for the treatment of retinopathy.

(6) The agent of (5), wherein the retinopathy is ischemic retinopathy.

(7) The agent of (6), wherein the ischemic retinopathy is diabetic retinopathy.

25 (8) The agent of any of (1) to (7), which is in the form of a preparation for local administration to the eye.

(9) A method for treating visual cell function disorder, comprising administering an effective amount of an interleukin 2 inhibitor to a subject in need of the treatment of visual cell function disorder.

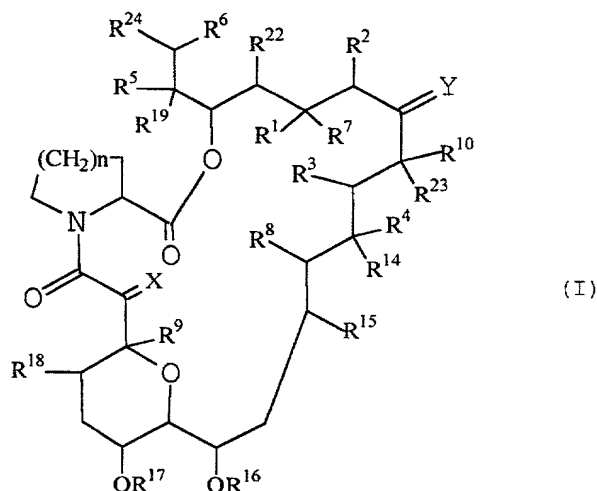
30 (10) Use of an interleukin 2 inhibitor for the production of a pharmaceutical composition for the treatment of visual cell function disorder.

DETAILED DESCRIPTION OF THE INVENTION

The IL-2 inhibitor to be used in the present invention is not particularly limited and may be any as long as it has an IL-2 inhibitory activity. One example

thereof is IL-2 production inhibitor. Other example is IL-2 signal transduction inhibitor. Preferable examples thereof include macrolide compounds such as FK506, Ascomycin derivative, Rapamycin derivative and the like and cyclosporins and the like.

- 5 Specific examples of macrolide compound include tricyclo compound (I) of the following formula and a pharmaceutically acceptable salt thereof.



wherein adjacent pairs of R¹ and R², R³ and R⁴, and R⁵ and R⁶ each independently
 a) consist of two adjacent hydrogen atoms, wherein R² is optionally alkyl, or
 b) form another bond optionally between carbon atoms binding with the
 members of said pairs ;

R⁷ is hydrogen atom, hydroxy, protected hydroxy or alkyloxy, or may form oxo with R¹ ;

R⁸ and R⁹ each independently show hydrogen atom or hydroxy ;

R¹⁰ is hydrogen atom, alkyl, alkyl substituted by one or more hydroxy, alkenyl, alkenyl substituted by one or more hydroxy or alkyl substituted by oxo ;

X is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula -CH₂O- ;

Y is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula N-NR¹¹R¹² or N-OR¹³ ;

R¹¹ and R¹² each independently show hydrogen atom, alkyl, aryl or tosyl ;

R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²² and R²³ each independently show hydrogen atom or alkyl ;

R^{24} is a optionally substituted ring that may contain one or more hetero atom(s) ; and

n is 1 or 2.

In addition to the meaning noted above, Y , R^{10} and R^{23} may show, together with the carbon atom they bind with, a saturated or unsaturated 5 or 6-membered heterocyclic group containing nitrogen atom, sulfur atom and/or oxygen atom, wherein the heterocyclic group may be substituted by one or more group(s) selected from alkyl, hydroxy, alkyloxy, benzyl, a group of the formula $-CH_2Se(C_6H_5)$, and alkyl substituted by one or more hydroxy.

Preferable R^{24} is, for example, cyclo(C_5 - C_7)alkyl optionally having suitable substituent, such as the following.

(a) 3,4-dioxocyclohexyl ;

(b) 3- R^{20} -4- R^{21} -cyclohexyl,

wherein R^{20} is hydroxy, alkyloxy or $-OCH_2OCH_2CH_2OCH_3$, and

R^{21} is hydroxy, $-OCN$, alkyloxy, heteroaryloxy having suitable substituent, $-OCH_2OCH_2CH_2OCH_3$, protected hydroxy, chloro, bromo, iodo, aminooxalyloxy, azide, p-tolyloxythiocarbonyloxy, or $R^{25}R^{26}CHCOO-$ (wherein R^{25} is hydroxy optionally protected where desired or protected amino, and R^{26} is hydrogen atom or methyl,

or R^{20} and R^{21} in combination form an oxygen atom of epoxide ring) ; or

(c) cyclopentyl wherein cyclopentyl is substituted by methoxymethyl, optionally protected hydroxymethyl where desired, acyloxymethyl (wherein acyl moiety is optionally quaternized dimethylamino or optionally esterified carboxy), one or more optionally protected amino and/or hydroxy, or aminooxalyloxymethyl. Preferable example includes 2-formyl-cyclopentyl.

The definition of each symbol used in the formula (I), specific examples thereof and preferable embodiments thereof are explained in detail in the following.

"Lower" means that a group has 1 to 6 carbon atoms unless otherwise indicated.

Preferable examples of the alkyl moiety of "alkyl" and "alkyloxy" include linear or branched fatty hydrocarbon residue, such as lower alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, neopentyl, hexyl and the like).

Preferable examples of "alkenyl" include linear or branched fatty

hydrocarbon residue having one double bond, such as lower alkenyl (e.g., vinyl, propenyl (e.g., allyl and the like), butenyl, methylpropenyl, pentenyl, hexenyl and the like.

Preferable examples of "aryl" include phenyl, tolyl, xylyl, cumenyl, mesityl, naphthyl and the like.

Preferable examples of the protective group for "protected hydroxy" and "protected amino" include 1-(loweralkylthio)(lower)alkyl such as lower alkylthiomethyl (e.g., methylthiomethyl, ethylthiomethyl, propylthiomethyl, isopropylthiomethyl, butylthiomethyl, isobutylthiomethyl, hexylthiomethyl and the like), with more preference given to C₁ - C₄ alkylthiomethyl and most preference given to methylthiomethyl;

tri-substituted silyl such as tri(lower)alkylsilyl (e.g., trimethylsilyl, triethylsilyl, tributylsilyl, tert-butyl dimethylsilyl, tri-tert-butylsilyl and the like), and lower alkyldiarylsilyl (e.g., methyldiphenylsilyl, ethyldiphenylsilyl, propyldiphenylsilyl, tert-butyldiphenylsilyl and the like, with more preference given to tri(C₁ - C₄)alkylsilyl and C₁ - C₄ alkyldiphenylsilyl, and most preference given to tert-butyl-dimethylsilyl, tert-butyldiphenylsilyl;

acyl such as fatty acyl derived from carboxylic acid, sulfonic acid and carbamic acid, fatty acyl substituted by aromatic acyl and aromatic, and the like.

The fatty acyl is exemplified by lower alkanoyl optionally having 1 or more suitable substituent(s) (e.g., carboxy) such as formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, carboxyacetyl, carboxypropionyl, carboxybutyryl, carboxyhexanoyl and the like ;

cyclo(lower)alkyloxy(lower)alkanoyl optionally having 1 or more suitable substituent(s) (e.g., lower alkyl) such as cyclopropyloxyacetyl, cyclobutyloxypropionyl, cycloheptyloxybutyryl, mentyloxyacetyl, mentyloxypropionyl, mentyloxybutyryl, mentyloxypentanoyl, mentyloxyhexanoyl and the like,

camphorsulfonyl ;

lower alkylcarbamoyl having one or more suitable substituent(s) such as carboxy or protected carboxy and the like, such as carboxy(lower)alkylcarbamoyl (e.g., carboxymethylcarbamoyl, carboxyethylcarbamoyl, carboxypropylcarbamoyl, carboxybutylcarbamoyl, carboxypentylcarbamoyl, carboxyhexylcarbamoyl) and

tri(lower)alkylsilyl(lower)alkyloxycarbonyl(lower)alkylcarbamoyl (e.g.,
 trimethylsilylmethoxycarbonylethylcarbamoyl,
 trimethylsilylethoxycarbonylpropylcarbamoyl,
 triethylsilylethoxycarbonylpropylcarbamoyl, tert-butyl
 5 dimethylsilylethoxycarbonylpropylcarbamoyl,
 trimethylsilylpropoxycarbonylbutylcarbamoyl).

Aromatic acyl is exemplified by aroyl optionally having suitable
 substituent(s) (e.g., nitro), such as benzoyl, toluoyl, xyloyl, naphthoyl, nitrobenzoyl,
 dinitrobenzoyl, nitronaphthoyl and the like ; and
 10 arenesulfonyl optionally having one or more suitable substituent(s) (e.g., halogen),
 such as benzenesulfonyl, toluenesulfonyl, xylenesulfonyl, naphthalenesulfonyl,
 fluorobenzenesulfonyl, chlorobenzenesulfonyl, bromobenzenesulfonyl,
 iodobenzenesulfonyl and the like.

The aliphatic acyl substituted by aromatic group may be, for example,
 15 ar(lower)alkanoyl optionally having one or more suitable substituent(s) (e.g., lower
 alkyloxy or trihalo(lower)alkyl and the like), wherein specific examples are
 phenylacetyl, phenylpropionyl, phenylbutyryl, 2-trifluoromethyl-2-methoxy-2-
 phenylacetyl, 2-ethyl-2-trifluoromethyl-2-phenylacetyl, 2-trifluoromethyl-2-
 propoxy-2-phenylacetyl and the like.

20 Of the above-mentioned acyl, more preferable acyl includes C₁ - C₄ alkanoyl
 optionally having carboxy, cyclo(C₅ - C₆)alkyloxy(C₁ - C₄)alkanoyl having two (C₁ -
 C₄)alkyl in the cycloalkyl moiety, camphorsulfonyl, carboxy (C₁ -
 C₄)alkylcarbamoyl, tri(C₁ - C₄)alkylsilyl(C₁ - C₄)alkyloxycarbonyl(C₁ -
 C₄)alkylcarbamoyl, benzoyl optionally having 1 or 2 nitro groups, and
 25 benzenesulfonyl having halogen, phenyl(C₁ - C₄)alkanoyl having C₁ - C₄ alkyloxy
 and trihalo(C₁ - C₄)alkyl. Of these, most preferred are acetyl, carboxypropionyl,
 mentyloxyacetyl, camphorsulfonyl, benzoyl, nitrobenzoyl, dinitrobenzoyl,
 iodobenzenesulfonyl, 2-trifluoromethyl-2-methoxy-2-phenylacetyl and the like.

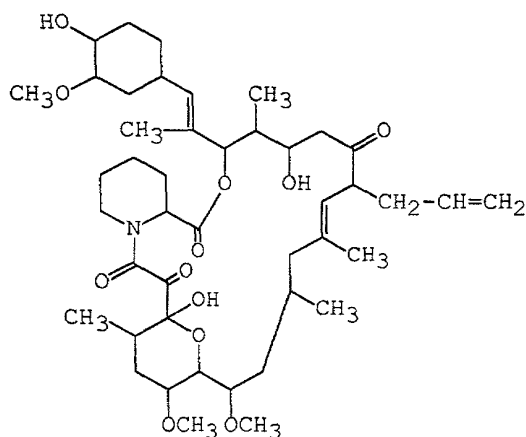
Preferable examples of the "heterocyclic group consisting of saturated or
 30 unsaturated 5 or 6-membered ring having nitrogen atom, sulfur atom and/or
 oxygen atom" are pyrrolyl, tetrahydrofuryl and the like.

The "heteroaryl optionally having a suitable substituent moiety" of the
 "heteroaryloxy optionally having a suitable substituent" is that exemplified for R¹ of

the compound of the formula I of EP-A-532,088, with preference given to 1-hydroxyethylindol-5-yl. The disclosure is incorporated hereinto by reference.

The tricyclo compound (I) and a pharmaceutically acceptable salt thereof to be used in the present invention have superior IL-2 inhibitory action and immunosuppressive action, antibacterial action and other pharmacological activity, so that they are useful for the prophylaxis and treatment of rejection in organ or tissue transplantation, graft versus host reaction, autoimmune diseases, infectious diseases and the like, as noted, together with the production method thereof, in, for example, EP-A-184162, EP-A-323042, EP-A-423714, EP-A-427680, EP-A-465426, EP-A-480623, EP-A-532088, EP-A-532089, EP-A-569337, EP-A-626385, WO89/05303, WO93/05058, WO96/31514, WO91/13889, WO91/19495, WO93/5059 and the like, all of these publications are hereby incorporated by reference.

In particular, the compounds called FR900506 (=FK506), FR900520 (Ascomycin), FR900523 and FR900525 are produced by the genus *Streptomyces*, such as *Streptomyces tsukubaensis*, No. 9993 (depository : National Institute of Bioscience and Human-Technology Agency of Industrial Science and Technology, the Ministry of International Trade and Industry, 1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki-ken, Japan (formerly : Fermentation Research Institute, Agency of Industrial Science and Technology, the Ministry of International Trade and Industry), date of deposit : October 5, 1984, deposit number : FERM BP-927 or *Streptomyces hygroscopicus subsp. Yakushimaensis*, No. 7238 (depository : National Institute of Bioscience and Human-Technology Agency of Industrial Science and Technology, 1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki-ken, Japan (formerly : Fermentation Research Institute, Agency of Industrial Science and Technology, the Ministry of International Trade and Industry), date of deposit : January 12, 1985, deposit number : FERM BP-928 (EP-A-0184162), and the compound of the following formula, FK506 (general name : Tacrolimus) is a representative compound.



Chemical name : 17-allyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxo-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone

Of the tricyclo compounds (I), more preferred is a compound wherein adjacent pairs of R³ and R⁴, and R⁵ and R⁶ each independently form another bond optionally between carbon atoms binding with the members of said pairs ;

R⁸ and R²³ each independently show hydrogen atom ;

R⁹ is hydroxy ;

R¹⁰ is methyl, ethyl, propyl or allyl ;

X is (hydrogen atom, hydrogen atom) or oxo ;

Y is oxo ;

R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹ and R²² each independently show methyl ;

R²⁴ is 3-R²⁰-4-R²¹-cyclohexyl,

wherein R²⁰ is hydroxy, alkyloxy or -OCH₂OCH₂CH₂OCH₃, and

R²¹ is hydroxy, -OCN, alkyloxy, heteroaryloxy having suitable substituent,

-OCH₂OCH₂CH₂OCH₃, protected hydroxy, chloro, bromo, iodo,

aminooxalyloxy, azide, p-tolyloxythiocarbonyloxy

or R²⁵R²⁶CHCOO- wherein R²⁵ is optionally protected hydroxy as desired,

or protected amino, and R²⁶ is hydrogen atom or methyl), or R²⁰ and R²¹ in

combination form an oxygen atom of epoxide ring; and

n is 1 or 2.

Particularly preferable tricyclo compound (I) include, besides FK506, Ascomycin derivatives such as halogenated derivative of 33-epi-chloro-33-desoxy Ascomycin described in Example 66a of EP-A-427,680 and the like.

Other preferable IL-2 inhibitors (macrolide compounds) include

- 5 Rapamycin described in MERCK INDEX, 12 edition, No. 8288 and derivatives thereof. Preferable examples thereof include O-substituted derivative described at page 1 of WO95/16691, formula A, wherein the 40th hydroxy is -OR₁ (wherein R₁ is hydroxyalkyl, hydroalkyloxyalkyl, acylaminoalkyl and aminoalkyl), such as 40-O-(2-hydroxy)ethyl Rapamycin, 40-O-(3-hydroxy)propyl Rapamycin, 40-O-[2-
- 10 (2-hydroxy)ethoxy]ethyl Rapamycin and 40-O-(2-acetaminoethyl)-Rapamycin. These O-substituted derivatives can be produced by reacting, under appropriate conditions, Rapamycin (or dihydro or deoxo Rapamycin) and an organic radical bound with leaving group (e.g., RX wherein R is an organic radical desirable as O-substituent, such as alkyl, allyl and benzyl moiety, and X is a leaving group such
- 15 as CCl₃C(NH)O and CF₃SO₃). The conditions are: when X is CCl₃C(NH)O, acidic or neutral conditions, such as in the presence of trifluoromethanesulfonic acid, camphorsulfonic acid, p-toluenesulfonic acid or their corresponding pyridinium or substituted pyridinium salt, and when X is CF₃SO₃, in the presence of a base such as pyridine, substituted pyridine, diisopropylethylamine and
- 20 pentamethylpiperidine. The most preferable Rapamycin derivative is 40-O-(2-hydroxy)ethyl Rapamycin as disclosed in WO94/09010, which is hereby incorporated into the specification by reference.

- The pharmaceutically acceptable salt of tricyclo compound (I), Rapamycin and derivatives thereof are nontoxic and pharmaceutically acceptable
- 25 conventional salts, which are exemplified by salts with inorganic or organic base such as alkali metal salt (e.g., sodium salt, potassium salt and the like), alkaline earth metal salt (e.g., calcium salt, magnesium salt and the like), ammonium salt, and amine salt (e.g., triethylamine salt, N-benzyl-N-methylamine salt and the like).

- In the IL-2 inhibitor of the present invention, particularly macrolide
- 30 compound, one or more pairs of stereoisomers, such as optical isomers and geometric isomers, may be included due to conformer or asymmetric carbon atom and double bond. Such conformers and isomers are also encompassed in the present invention. In addition, macrolide compounds can form solvates, which

case is also encompassed in the present invention. Preferable solvate is exemplified by hydrates and ethanolates.

Other IL-2 inhibitors are known from MERCK INDEX, 12th ed., No. 2821, US Patent Nos. 4,117,118, 4,215,199, 4,288,431, 4,388,307, Helv. Chim. Acta, 60, 1568 (1977) and 65,1655 (1982) and Transplant. Proc. 17, 1362 (1985) and the like. Specifically, they are cyclosporins such as cyclosporin A, B, C, D, E, F and G and derivatives thereof. Particularly preferred is cyclosporin A. These are hereby incorporated into the specification by reference.

The tricyclo compound (I), pharmaceutically acceptable salt thereof, cyclosporins and derivatives thereof can be classified as "IL-2 production inhibitor" that inhibit production of IL-2. Rapamycin and derivative thereof can be classified as "IL-2 signal transduction inhibitor" that inhibit transmission of IL-2 signal.

In the present invention, visual cell function disorder means the state where visual cell of retina is suffering from disorder in the function for a certain reason, which can be specifically confirmed by the variation of peak latency or amplitude of a-wave in ERG as compared to those in the normal state. Inasmuch as the visual cell function disorder is caused by various retinal disorders such as degenerative retinopathy, retinochoroidal disorders and the like, the agent of the present invention for the treatment of visual cell function disorder can be used for treating retinopathy. In particular, the agent for treating visual cell function disorder of the present invention has superior action of improving visual cell function disorder, as is evident from the experimental example to be mentioned later, in ischemic retinopathy models, and can be used for the treatment of ischemic retinopathy. The ischemic retinopathy is caused by various reasons. For example, retinovascular diseases are caused by systemic disease, such as diabetes, hypertension and arteriosclerosis, and are exemplified by diabetic retinopathy, fundus hypertonicus, as well as local vascular disorders in retina, such as central retinal artery occlusion, central retinal vein thrombosis, retinal peripheral vascular occlusion, retinopathy of prematurity and the like.

The treatment in the context of the present invention includes any management such as prevention, treatment, alleviation of symptom, reduction of symptoms, prevention of progression and the like.

The interleukin 2 inhibitor to be used in the present invention can be used as a pharmaceutical agent for human and animals, and can be administered systemically or locally by oral administration, intravenous administration (inclusive of transfusion), subcutaneous administration, rectal or vaginal administration, administration to local site of the eye (inclusive of eye ointment). In consideration of systemic influence, significant expression of the effect and the like, it is particularly preferably used in the form for local administration to the eye.

The dose of the interleukin 2 inhibitor varies depending on the kind, age, body weight of the administration object such as human and animal, condition to be treated, desired therapeutic effect, administration route, treatment method, treatment period and the like. Generally, when it is administered systemically, the dose is about 0.0001 – 1000 mg, preferably 0.001 – 500 mg, which is given in a single dose or 2 to 4 doses a day or in a sustained manner. When it is administered locally to the eye, a preparation containing the active ingredient in a proportion of 0.001 – 10.0 w/v%, preferably 0.005 – 5.0 w/v%, is applied several times a day per eye, preferably instilled or applied 1 to 6 times a day.

According to the present invention, an interleukin 2 inhibitor, which is an active ingredient, can be administered alone or in combination with other pharmacologically active components. When administered after formulating a preparation, it can be administered as a preparation produced by a conventional method. The dosage form may be, for example, eye drop, eye ointment, powder, granule, tablet, capsule, injection, ointment and the like, with particular preference given to eye drop and eye ointment. Such preparation can be produced according to a conventional method. Of such preparations, an oral preparation is preferably a solid solution preparation produced in the same manner as in the preparation of EP-A-0240773. When an eye drop is desired, an eye drop as described in EP-A-0406791 is preferable. When desired, additives generally used for eye drop such as isotonicizing agent (e.g., sodium chloride), buffer (e.g., boric acid, phosphoric acid-sodium hydrogen, sodium dihydrogenphosphate and the like), preservative (e.g., benzalkonium chloride, benzetonium chloride, chlorobutanol and the like), tackifier [e.g., sugar (lactose, mannitol, maltose sugar and the like), hyaluronic acid (sodium hyaluronate, potassium hyaluronate and the like), a salt thereof, mucopolysaccharide (chondroitin sulfate and the like),

sodium polyacrylate, vinyl carboxy polymer, crosslinked polyacrylate, and the like may be added. These are hereby incorporated into the specification by reference.

The present invention is explained in more detail in the following by way of Examples, to which the present invention is not limited.

5 • Examples

Experimental Example 1 Effect on changes in ERG of rats with retinal ischemia

An ischemic state was induced by ligating the retinal blood vessel of rat and reperfusion to make ischemic retinopathy model in rat, with which the effect on changes in retinal potential was tested.

10 (1) Test animal

Long Evans colored rats (male, 7- or 8-week-old when received : body weight 200 - 250 g) were prebred for 8 days and the animals free of abnormality in general conditions, such as body weight, were used for the test.

(2) Test substance and administration method

15 As the active ingredient in the present invention, FK506 was used and the following 0.1% eye drop (suspension) was used as a test drug.

Test drug

Suspension having the following composition which was prepared in the same manner as in EP-A-0406791 (Example 6)

20	FK506	1.0 mg
	polyvinyl alcohol	7.0 mg
	disodium hydrogenphosphate 12 hydrate	0.05 mg
	sodium dihydrogenphosphate 2 hydrate	0.76 mg
	phosphoric acid	appropriate amount
25	sodium hydroxide	appropriate amount
	sodium chloride	8.56 mg
	benzalkonium chloride	0.1 mg
	injectable water	appropriate amount

30	Total amount	1 ml
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As the control, the base agent of an eye drop without the active ingredient was used. The test drug was instilled to the eye by 10 μ l/eye using a micropipette

3 times a day (8 : 00, 13 : 00, 18 : 00) from day 1 to day 7 of the test. The control agent was also administered by instillation in the same manner.

(1) preparation of ischemic retinopathy model

At day 8 of the test, the rats were anesthetized by intraperitoneal administration of diazepam (0.625 mg/kg), and pentobarbital (20 mg/kg) and a part of periorbita was removed from the side. A pedicle consisting of optic nerve, ophthalmic artery and ophthalmic vein was removed and the whole pedicle was ligated to cause ischemia. The ischemia was continued for 45 minutes and reperused by releasing the ligation.

(2) ERG determination

The apparatus and parameter were standarized by the following.
"Standard for Clinical Electroretinography" (International Standardization Committee)

Apparatus :

The Electrophysiologic Personal Interfaced Computer-2000 (LKC Technologies Incorporated)

ERG determination parameter :

amplifier

high pass filter : 500 Hz

low pass filter : 0.3 Hz

notch filter : off

amplitude : 50 μ V/division (maximum 1500 μ V)

time : 20 ms/division (maximum 2500 ms)

cornea electrode

impedance : 10 to 20 K Ω

optical stimulation

single flash : 15 ms

intensity : 2.289 cd. s.m⁻²

ganzfeld

filter : none

ERG was determined with the lapse of time before and after ischemia under the above-mentioned conditions.

(3) results

Taking the ERG before ischemia as 100%, the ratio thereto of the peak latency of the a-wave after reperfusion was determined. It disappeared immediately after reperfusion. The results are shown in Table 1.

Table 1

Administration group	(n)	a-wave peak latency (% average \pm SD)		
		60 min after reperfusion	90 min after reperfusion	120 min after reperfusion
Control drug	(8)	195.6 \pm 53.5	190.8 \pm 55.3	191.9 \pm 60.4
Test drug	(8)	137.1 \pm 47.1*	141.6 \pm 44.8*	134.4 \pm 31.6*

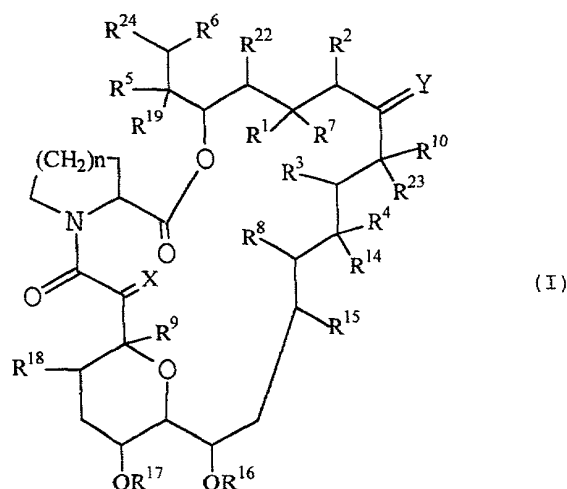
* P<0.05 (comparison to control drug by ANOVA detection)

5 The a-wave peak latency disappeared immediately after reperfusion, but peak latency was prolonged with the lapse of time thereafter. As is evident from Table 1, the test drug administration group significantly suppressed the prolongation of the a-wave peak latency as compared to the control drug group.

10 This application is based on application No. 60/113,939 filed in United States of America, the content of which is incorporated hereinto by reference.

CLAIMS

1. An agent for treating visual cell function disorder comprising an interleukin 2 inhibitor as an active ingredient.
2. The agent of claim 1, wherein the interleukin 2 inhibitor is a macrolide compound or a cyclosporin.
3. The agent of claim 2, wherein the macrolide compound is a tricyclo compound (I) of the following formula



wherein adjacent pairs of R^1 and R^2 , R^3 and R^4 , and R^5 and R^6 each independently

- a) consist of two adjacent hydrogen atoms, wherein R^2 is optionally alkyl, or
- b) form another bond optionally between carbon atoms binding with the members of said pairs ;

R^7 is hydrogen atom, hydroxy, protected hydroxy, or alkyloxy, or optionally form oxo with R^1 ;

R^8 and R^9 each independently show hydrogen atom or hydroxy ;

R^{10} is hydrogen atom, alkyl, alkyl substituted by one or more hydroxy, alkenyl, alkenyl substituted by one or more hydroxy or alkyl substituted by oxo ;

X is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $-CH_2O-$;

Y is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $N-NR^{11}R^{12}$ or $N-OR^{13}$;

R¹¹ and R¹² each independently show hydrogen atom, alkyl, aryl or tosyl ;

R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²² and R²³ each independently show hydrogen atom or alkyl ;

R²⁴ is a ring that is optionally substituted and optionally contain one or more
5 hetero atom(s) ; and

n is 1 or 2,

wherein Y, R¹⁰ and R²³ optionally show, together with the carbon atom
they bind with, a saturated or unsaturated 5 or 6-membered heterocyclic
group containing nitrogen atom, sulfur atom and/or oxygen atom, the
10 heterocyclic group being optionally substituted by one or more group(s)
selected from the group consisting of alkyl, hydroxy, alkyloxy, benzyl, a
group of the formula -CH₂Se(C₆H₅), and alkyl substituted by one or more
hydroxy,

or a pharmaceutically acceptable salt thereof.

15 4. The agent of claim 2 or claim 3, wherein the macrolide compound is FK506.

5. The agent of any of claim 1 to claim 4, which is used for the treatment of
retinopathy.

20 6. The agent of claim 5, wherein the retinopathy is ischemic retinopathy.

7. The agent of claim 6, wherein the ischemic retinopathy is diabetic retinopathy.

25 8. The agent of any of claim 1 to claim 7, which is in the form of a preparation for
local administration to the eye.

9. A method for treating visual cell function disorder, comprising administering
an effective amount of interleukin 2 inhibitor to a subject in need of the treatment
30 of visual cell function disorder.

10. Use of interleukin 2 inhibitor for the production of a pharmaceutical
composition for the treatment of visual cell function disorder.

Declaration, Power of Attorney and Petition

Page 1 of 2

WE (I) the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name,

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

AGENT FOR TREATING VISUAL CELL FUNCTION DISORDER

the specification of which

- ☒ is attached hereto.
☐ was filed on _____ as
Application Serial No. _____
and amended on _____ .
☒ was filed as PCT international application
Number PCT/JP99/07161
on December 20, 1999,
and was amended under PCT Article 19
on _____ (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information known to be material to the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under 35 U.S.C. § 1 19(a)-(d) or § 365(b,) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. Prior Foreign Application(s)

Application No.	Country	Day/Month/Year	Priority Claimed	
_____	_____	_____	<input type="checkbox"/> Yes	<input type="checkbox"/> No
_____	_____	_____	<input type="checkbox"/> Yes	<input type="checkbox"/> No
_____	_____	_____	<input type="checkbox"/> Yes	<input type="checkbox"/> No
_____	_____	_____	<input type="checkbox"/> Yes	<input type="checkbox"/> No

100

(Filing Date)

Status (pending, patented,
abandoned)

pending

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.